PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 229/46, 229/50, C07D 307/87, 333/62, 257/04, A61K 31/195, 31/19, 31/38, 31/34, 31/41

A1

(11) International Publication Number: WO 96/15099

(43) International Publication Date: 23 May 1996 (23.05.96)

(21) International Application Number: PCT/DK94/00421

(22) International Filing Date: 9 November 1994 (09.11.94)

(71) Applicant *(for all designated States except US)*: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PELLICCIARI, Roberto [IT/IT]; Via U. Rocchi, 60, I-06123 Perugia (IT). LUNEIA, Roberto [IT/IT]; Via Foligno, 2, I-06058 San Terenziano (IT). LOMBARDI, Grazia [IT/IT]; Via S. Marta, 21, I-50139 Firenze (IT). MORONI, Flavio [IT/IT]; Viale Machiavelli, 7, I-50125 Firenze (IT).

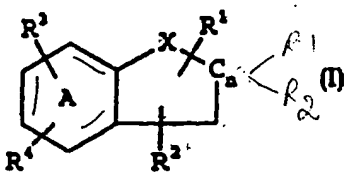
(74) Agent: KINDTLER, Jens; Novo Nordisk a/s, Novo Allé, DK-2880 Bagsvaerd (DK).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

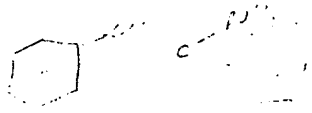
Published
With international search report.

(54) Title: HETEROCYCLIC COMPOUNDS, THEIR PREPARATION AND USE

(57) Abstract



The present invention relates to therapeutically active heterocyclic compounds of formula (I) wherein n is 0, 1 or 2; and X is -O-, -S, -N(R^5)- or -CH_2-; and R^1 is H, NH_2, NHR^5 or OH; and R^2 and R^3 independently are H, COOH, $COOR^5$, $CONH_2$, $CONHR^5$, $CON(R^5)_2$, $CONHSO_2R^5$ or tetrazole; and R^4 is H, OH, NH_2, NHR^5, CF_3, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-6}-cycloalkyl, phenyl or C_{1-4}-alkoxy; and R^5 is H, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, phenyl or C_{3-6}-cycloalkyl; and ring A can be partly or completely saturated or aromatic, or a salt thereof with a pharmaceutically acceptable acid or base, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in treating diseases in the central nervous system related to the metabotropic glutamate receptor system.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

Heterocyclic compounds, their preparation and use

The present invention relates to therapeutic active amino acids, a method for preparing the same, pharmaceutical compositions comprising the compounds and a method of treating therewith.

Recent molecular biological studies have clearly established the existence of two major types of glutamate receptors in the central nervous system namely the ionotropic and the metabotropic glutamate receptors. The latter is characterised by being G-protein-linked to changes in second messenger formation and modulation of ion channel function, (Meldrum, B. (1991) Epilepsy Res. 10, 55-61, Chapman, A. (1991) in Excitatory Amino Acids p. 265-286, Blackwell scientific publ. ltd., Oxford).

At present 6 different subtypes of the metabotropic glutamate receptors are described ($MGluR_1$ to $MGluR_6$) and in addition some spliced variants of the subtypes are reported.

The Metabotropic glutamate receptor subtypes $MGluR_1$ and $MGluR_5$ are coupled to phosphoinositide hydrolysis (Johnson, G. and Bigge, C.F. (1991) Annu. Rep. Med. Chem. 26, 11-22, Hansen, J.J. and Krogsgaard-Larsen, P. Med. Res. Rev. 10,55-94, Thomsen, C. and Suzdak, P. (1993) Eur. J. Pharmacol. 245 ,299), while the others are coupled to cyclic AMP formation (Schoepp, D.D., Johnson, B.G. and Monn, J.A. (1992) J. Neurochem. 58, 1184-1186, Cartmell et al. (1992) J. Neurochem. 58, 1964-1966, Manzoni, O. et al. (1992) Eur. J. Pharmacol. 225, 357-358).

Compounds such as L-glutamate, quisqualate and ibotenate are known to act as non-selective agonists on the metabotropic glutamate receptors, while selective ionotropic glutamate receptor agonists such as NMDA, AMPA and kainate do have little effect on these receptors.

Recently a few compounds without activity at the ionotropic glutamate receptors but with activity at the metabotropic receptors have been identified.

These comprise trans-ACPD (trans 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid), the partial agonist L-AP3 (L-2-amino-3-phosphonopropionic acid) (Palmer, E., Monaghan, D.T. and Cotman, C.W. (1989) Eur. J. Pharmacol. 166, 585-587, Desai, M.A. and Conn, P.J. (1990) Neurosci. Lett. 109, 157-162, Schoepp, D.D. et al. (1991), J. Neurochem. 56, 1789-1796, Schoepp D.D. and Johnson B.G. (1989), J. Neurochem. 53,1865-1613), L-AP4 (L-2-amino-4-phosphonobutyrate) which is an agonist at the $MGluR_4$ receptor (Thomsen C. et al. (1992), Eur. J. Pharmacol. 227, 361-362) and some of the isomers of CCG (2-(carboxycyclopropyl)glycines) especially L-CCG-I and L-CCG-II (Hayashi, Y. et al. (1992), Br. J. Pharmacol. 107, 539-543).

Very few selective antagonists at the metabotropic glutamate receptors have been reported, however some phenylglycine derivatives S-CPG (S-4-carboxyphenyl glycine), S-4C3HPG (S-4-carboxy-3-hydroxyphenyl glycine) and S-MCPG (S-alpha methyl-4-carboxyphenyl glycine) have been reported to antagonise trans ACPD stimulated phosphoinositide hydrolysis and thus possibly acting as antagonists at the metabotropic glutamate receptors at the subtypes $MGluR_1$ and $MGluR_5$ (Thomsen, C. and Suzdak, P, (1993) Eur. J. Pharmacol. 245, 299).

Literature evidence suggests that compounds selective for the metabotropic glutamate receptors either as agonists or antagonists are useful in the treatment of different neurological diseases.

The use of compounds active at the metabotropic glutamate receptors for

the treatment of epilepsy is corroborated by investigations of the influence of trans-ACPD in the formation of convulsions (Sacaan and Schoepp, (1992), Neurosci. lett. 139, 77) and that phosphoinositide hydrolysis mediated via MGluR is increased after kindling experiments in rats (Akiyama et al. (1992),Brain Res. 569, 71).

Trans-ACPD has been shown to increase release of dopamine in the rat brain which indicates that compounds acting on the metabotropic glutamate receptors might be usable for the treatment of Parkinson's disease and Huntington's Chorea (Sacaan et al. (1992), J. Neurochem. 59, 245).

The use of compounds active at the metabotropic glutamate receptors for treatment of neurological diseases such as senile dementia has been indicated by the findings of Zheng and Gallagher ((1992), Neuron 9, 163) and Bashir et al. ((1993), Nature 363, 347) who demonstrated that activation of metabotropic glutamate receptors are necessary for the induction of long term potentiation (LTP) in nerve cells (septal nucleus,hippocampus) and the finding that long term depression is induced after activation of metabotropic glutamate receptors in cerebellar granule cells (Linden et al. (1991), Neuron 7,81).

Investigations also show that in the treatment of deficiencies of mental and motoric performance seen after conditions of brain ischemia the metabotropic glutamate receptor active compounds may prove usable.

Trans-ACPD has been shown to be a neuroprotective agent in an MCAO model in mice (Chiamulera et al. (1992), Eur. J. Pharmacol. 215, 353), and it has been shown to inhibit NMDA induced neurotoxicity in nerve cell cultures (Koh et al., (1991), Proc. Natl. Acad. Sci. USA 88, 9431).

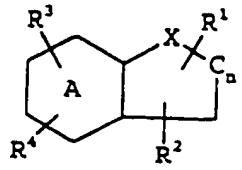
Also in the treatment of pain the metabotropic glutamate receptor active

compounds seem of interest, proved by the fact that antagonists at the metabotropic glutamate receptors antagonises sensory synaptic response to noxious stimuli of thalamic neurons (Eaton, S.A. et al. (1993), Eur. J. Neurosci. 5, 186).

The above findings support that compounds acting on the metabotropic glutamate receptors are useful for the treatment of epilepsy, neurological diseases such as senile dementia, Parkinson's disease, Huntington's Chorea, pain and deficiencies of mental and motoric performance seen after conditions of brain ischemia.

We have now discovered a series of new amino acids which are potent antagonists at the metabotropic glutamate receptors.

The present invention relates to compounds of formula I



(I)

wherein

n is 0, 1 or 2; and

X is -O-, -S, -N(R^5)- or -CH_2-; and

R^1 is H, NH_2, NHR^5 or OH; and

R^2 and R^3 independently are H, COOH, $COOR^5$, $CONH_2$, $CONHR^5$, $CON(R^5)_2$, $CONHSO_2R^5$ or tetrazole; and

R^4 is H, OH, NH_2, NHR^5, CF_3, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-6}-

cycloalkyl, phenyl or C_{1-4}-alkoxy; and
R^5 is H, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, phenyl or C_{3-6}-cycloalkyl; and
ring A can be partly or completely saturated or aromatic,
or a salt thereof with a pharmaceutically acceptable acid or base.

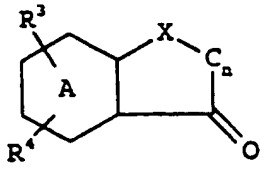
These salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, mandelic, benzoic, cinnamic, methanesulfonic, ethane sulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

Alkyl, alkenyl and alkynyl are intended to mean a straight or branched alkyl, alkenyl or alkynyl chain.

It is to be understood that the invention extends to each of the stereoisomeric forms of the compounds of formula I as well as the racemates.

The invention also relates to a method of preparing the above mentioned compounds. These methods comprise

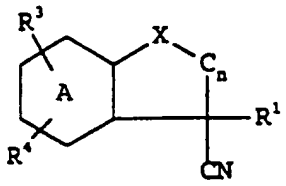
a) reacting a compound of the formula II



(II)

prepared by well known methods, wherein X, n, R^3, R^4 have the meanings defined above with reagents well known for converting oxo groups to amino acids or hydroxy acids either through hydantoin formation, through hydroxy nitrile or through aminonitrile formation, or

b) reacting a compound of the formula III



(III)

NO

wherein X, n, R^1, R^3 and R^4 have the meanings defined above with reagents known to transform a cyano group into a R^2 group wherein R^2 has the meaning defined above provided that R^2 must not be H.

Examples of the compounds of formula I are the following:

3-amino-2,3-dihydrobenzo[b]furane-3,6-dicarboxylic acid,
3-amino-2,3-dihydrobenzo[b]furane-3,7-dicarboxylic acid,
3-amino-2,3-dihydroindole-3,6-dicarboxylic acid,
3-amino-2,3-dihydroindole-3,7-dicarboxylic acid,
3-amino-1-methyl-2,3-dihydroindole-3,6-dicarboxylic acid,
3-amino-1-propyl-2,3-dihydroindole-3,7-dicarboxylic acid,
3-methylamino-1-ethyl-2,3-dihydroindole-3,6-dicarboxylic acid,
3-amino-2,3-dihydrobenzo[b]thiophene-3,6-dicarboxylic acid,
3-hydroxy-2,3-dihydrobenzo[b]thiophene-3,7-dicarboxylic acid,
1-amino-1-(5-tetrazolyl)indane-5-carboxylic acid,
methyl 1-amino-1-(5-tetrazolyl)indane-6-carboxylate.

The pharmacological properties of the compounds of the invention can be illustrated by determining their effects in different conventional radioligand binding assays or in functional in vitro assays.

The compounds of the invention were studied in an in vitro assay for measuring inhibition of PI-hydrolysis in BHK 570 cells expressing $mGluR_1\alpha$ receptors.

Principle

The metabotropic glutamate receptor (mGluR) is selectively activated by trans-aminocyclopentane dicarboxylic acid and is coupled to the hydrolysis of inositol phosphates via a GTP-binding protein. At the molecular level, cDNAs encoding six subtypes of the mGluR family have been isolated. The first subtype isolated (Houamed et al., 1991, Science 252, 1318), termed the mGluR1α, has been shown to be coupled to PI-hydrolysis when expressed in baby hamster kidney cells (BHK) (Thomsen et al., Brain Res. (in press)). In these cells no stimulation by 1 mM quisqualate or glutamate was observed with control BHK cells whereas a 6-8 fold increase over basal PI-hydrolysis was seen with BHK cells expressing mGluR1α.

Cell culture

BHK570 cells expressing mGluR1α are cultured in DMEM (4.5 g/l glucose, 2mM glutamin); 5% foetal calf serum; 0.10 mg/ml neomycin; 0.5 mg/ml G418; 1 μM methotrexate; 50 μg/ml gentamycin. Cells are subcultured every 5 days using 0.05% trypsin/EDTA in PBS.

Inositol phosphate formation

The protocol for PI-hydrolysis was measured using a modification of a method previously described (Berridge et al., 1982, Biochem. J. 206,587). Cells were plated in 16 mm wells (24 well multidish, Costar) with 1 confluent

100 mm dish per multidish. Replace the medium 24 h before the experiment with 500 µl fresh growth medium containing 4µCi/ml myo-[2-^{3}H]inositol (specific activity 18 Ci/mmol, Amersham). The cells were washed twice with Krebs-Henseleit buffer (Sigma cat. # 3753: glucose 2.0 g/l, $MgSO_4$ 0.141 g/l, $KHPO_4$ 0.16 g/l, KCl 0.35 g/l, NaCl 6.90 g/l and $NaHCO_3$ 2.1 g/l) supplemented with 10 mM LiCl and 2.5 mM $CaCl_2$. The buffer was equilibrated with 5% CO_2, 95% air to pH 7.5 at 37°C. Following 5 min of preincubation in the above buffer, buffer or test compounds were added and cells were incubated for 30 min at 37°C. In antagonist studies, add test compounds 5 min prior to agonist stimulation. PI-formation was stopped by placing the cells on ice and quickly aspirating the media. The wells were washed once with ice-cold Krebs-Henseleit buffer and subsequently 1 ml ice-cold 10% perchloric acid was added to each well. Place the cells on ice for 20 min. In Nunc minisorp test tubes (75 x 12 mm, cat. # 443990): add 250 µl of 10 mM EDTA, pH 7.0 + 5% Universal Indicator (Merck). Transfer the PCA extract to each tube containing the pH-indicator. Neutralize the samples with 1.5 M KOH + 60 mM HEPES to pH 7.5 (~ 1100-1200 µl). Centrifugate (6.000 rpm, 5 min, 0°C). They can be stored frozen at this point. Fractions of inositolphosphates were separated using ion-exchange columns (Amersham, RPN 1908) according to the method provided by Amersham.

Separation of inositol phosphates on ion-exchange columns

Prepare columns with 5 ml 1 M $KHCO_3$ and wash with 15 ml dist. water. Adjust vacuum so that the flow-rate does not exceed 5 ml/min.
Add 4 ml dist. water and subsequently 1 ml [^{3}H]InsP sample. Wash with 5 ml dist. water. IP1 to IP4 fractions may be collected with 5 ml 0.05; 0.10; 0.17 and 0.25 M $KHCO_3$, respectively. Usually IP1 and IP2 fractions are collected simultaneously. Scintillation liquid: use 12-15 ml Ultima Gold (Packard).

Testprocedure

Testcompounds are dissolved in DMSO, DMSO and Pluronic F-127 or ethanol and diluted in assay buffer. Glutamate (10 μM and 1000 μM) and buffer alone are included as a control.

Results

The stimulation by 10 μM shall represent a submaximal stimulation. The response by 10 μM glutamate should exceed 3-fold the basal level and should be below maximal stimulation (glutamate at 1 mM). The results are calculated relative to be stimulation by 10 μM glutamate and a dose response curve is generated.

Examples of test results obtained by testing some compounds of the present invention in the above mentioned assay appear from the following Table 1.

Table 1

Compound No.	IC_{50} (uM)
7	10
25	50

The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 10 mg to about 70 mg per day. In choosing a regimen for patients suffering from a disease in the central nervous system related to the metabotropic glutamate receptor system it may frequently be necessary to begin with a dosage of

from about 30 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously

react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph. Eur.

The invention will now be described in further detail with reference to the following examples.

EXAMPLE 1

5-Acetylindan (1)

$AlCl_3$ (1.706 g, 12.8 mmol) was added portionwise in 20 min to a solution of indan (1.50 g, 12.7 mmol) and AcCl (0.996 g, 12.7 mmol) in benzene (7.6 ml) kept under vigorous magnetic stirring at 0°C in an argon atmosphere. The resulting mixture was reacted at room temperature for 2 h after which cold (0°C) water was added (30 ml). The reaction mixture was then acidified with 3N HCl and extracted with AcOEt (3x20 ml). The combined organic phases were washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 1 as a yellow oil (2 g) which was used in the next step without any further purification; ^{1}H-NMR ($CDCl_3$) δ 2.10 (2H, q, J= 7.2 Hz, 2-CH_2), 2.56 (3H, s, Mc), 2.93 (4H, t, J= 7.2 Hz, 1-CH_2 and 3-CH_2), 7.26 (1H, d, J= 8.3 Hz, 7-CH), 7.80 (1H, d, J= 8.3 Hz, 6-CH), 7.85 (1H, s, 4-CH).

Indan-5-carboxylic acid (2)

Br_2 (5.89 g, 36.85 mmol) was added to a cold (0°C), magnetically stirred solution of KOH (6.9 g, 123.2 mmol) in water (25 ml). 1 (1.50 g, 9.36 mmol) was added dropwise in 5 min to this solution and the resulting mixture was heated at 40°C under stirring for 2 h. The reaction mixture was then diluted with ether (20 ml), the aqueous layer separated, added with MeOH (100 ml) and, after acidification with 6N HCl, extracted with $CHCl_3$ (3x30 ml). The combined organic phases were washed with water (30 ml), brine (30 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 2 as a white-yellow solid (1.0 g, 66%), mp 165-8°C; ^{1}H-NMR ($CDCl_3$) δ 2.13 (2H, q, J= 7.4 Hz, 2-CH_2), 3.00 (4H, t, J= 7.4 Hz, 1-CH_2 and 3-CH_2), 7.32 (1H, d, J= 8.5 Hz, 7-CH), 7.90 (1H, d, J= 7.8 Hz, 6-CH), 7.95 (1H, s, 4-CH).

Methyl indan-5-carboxylate (3)

An etheral solution of diazomethane (90 ml, from 16 g of Diazald™) was added to a cold (0°C) solution of 2 (3.0 g, 18.5 mmol) in ether (50 ml) and the resulting solution was magnetically stirred at room temperature for 30 min. Acetic acid (20 ml) was then added and the resulting mixture was washed with water (2x30 ml). Evaporation of the solvent gave a residue (3.2 mg) which was submitted to flash chromatography: elution with light petroleum-AcOEt 9:1 afforded 3 (3.0 g, 92%) as a yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.15 (2H, q, J= 7.5 Hz, 2-CH_2), 2.95 and 3.00 (4H, 2t, J= 7.5 Hz, 1-CH_2 and 3-CH_2), 3.90 (3H, s, Mc), 7.25 (1H, d, J= 7.8 Hz, 7-CH), 7.85 (1H, d, J= 7.8 Hz, 6-CH), 7.90 (1H, s, 4-CH).

Methyl 1-oxoindane-5-carboxylate (4) and methyl 1-oxoindane-6-carboxylate (5)

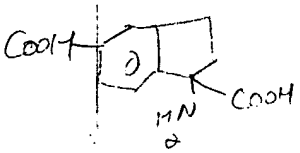
A solution of Cr_2O_3 (7.0 g, 70 mmol) in glacial AcOH (27 ml) and water (11.6 ml) was added dropwise in 30 min. to a magnetically stirred solution of 3 (5.0 g, 28.4 mmol) in glacial AcOH (13.5 ml) at room temperature. Stirring was continued for 36 h after which the reaction mixture was diluted with water (60 ml) and extracted with AcOEt (4x50 ml). The combined organic phases were washed with 10% K_2CO_3 (3x30 ml), brine (30 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (4.8 mg) which upon flash filtration on silica gel allowed the recovery of starting material 3 (0.5 g) and of a mixture of 4 and 5 (4 g). This mixture was then submitted to medium pressure chromatography: elution with light petroleum-AcOEt 85:15 yielded 4 (1.4 g, 26%) as a white solid, mp 110.8°C; ^{1}H-NMR ($CDCl_3$) δ 2.78 (2H, t, J= 6 Hz, 2-CH_2), 3.22 (2H, t, J= 6 Hz, 3-CH_2), 3.97 (3H, s, Mc), 7.82 (1H, d, J= 8 Hz, 7-CH), 8.05 (1H, d, J= 8 Hz, 6-CH), 8.18 (1H, s, 4-CH). Further elution with the same solvent gave 5 (1.6 g, 30%) as a white solid, mp 111.9°C;^{1}H-NMR ($CDCl_3$) δ 2.75 (2H, t, J= 6.3

Hz, 2-CH_2), 3.22 (2H, t, J= 6.3 Hz, 3-CH_2), 3.95 (3H, s, Me), 7.55 (1H, d, J= 7.6 Hz, 7-CH), 8.25 (1H, d, J= 7.6 Hz, 6-CH), 8.42 (1H, s, 4-CH).

Hydantoin of 4 (6)

KCN (0.424 g, 6.5 mmol) and $(NH_4)_2CO_3$ (1.35 g, 14.0 mmol) were added to a solution of 4 (0.620 g, 3.26 mmol) in DMF (6.2 ml) and water (0.5 ml) and the resulting mixture was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with AcOEt (30 ml), washed with saturated Na_2CO_3 (5x20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (0.62 g) was submitted to flash chromatography: elution with $CHCl_3$-McOH 96:4 yielded 6 (0.490 g, 58%) as a pale yellow solid, mp 112°C; ^{1}H-NMR ($CDCl_3$) δ 2.25 (1H, m, 2-CHa), 2.70 (1H, m, 2-CHb), 2.95-3.30 (2H, m, 3-CH_2), 3.90 (3H, s, Me), 7.22 (1H, d, J= 7.8 Hz, 7-CH), 7.88 (1H, d, J= 7.8 Hz, 6-CH), 7.90 (1H, s, 4-CH).

1-Aminoindan-1,5-dicarboxylic acid (7)

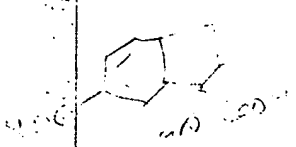


A mixture of 6 (0.650 g, 2.5 mmol), $Ba(OH)_2$ octahydrate (0.520 g, 1.7 mmol) and water (9.5 ml) was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3x15 ml). CO_2 was then bubbled into the aqueous layer, the resulting precipitate was centrifuged and the supernatant was neutralized with 3N HCl. The neutral solution was submitted to ion exchange resin chromatography on Dowex 50x2 200 and elution with 10% pyridine to give a solid which was further purified by reversed phase medium pressure chromatography: elution with McOH-water 6:4 afforded 7 (0240 g, 43%) as a white solid, mp>300°C; ^{1}H-NMR (D_2O) δ 2.20 (1H, m, 2-CHa), 2.50 (1H, m, 2-CHb), 2.95 (2H, t,J= 7.8 Hz, 3-CH_2), 7.05 (1H, d, J= 7.8 Hz, 7-CH), 7.55 (1H, d, J= 7.8 Hz, 6-CH), 7.60 (1H, s, 4-CH); ^{13}C-NMR (D_2O) δ 30.42, 35.50, 68.70, 123.00, 127.20, 129.50, 132.50, 142.90, 146.00, 169.90, 172.70.

Hydantoin of 5 (8)

NaCN (0.695 g, 14,18 mmol) and $(NH_4)_2CO_3$ (2.94 g, 30.4 mmol) were added to a solution of 5 (1.35 g, 7.10 mmol) in DMF (13.5 ml) and water (1.2 ml) and the resulting mixture was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with AcOEt (50 ml), washed with saturated Na_2CO_3 (5x30 ml), brine (30 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (90 g) was submitted to flash chromatography: elution with $CHCl_3$-MeOH 96:4 yielded 8 (0.790 g, 43%) as a pale yellow solid, mp 112°C; ^{1}H-NMR ($CDCl_3$+CD_3OD) δ 2.35 (1H, m, 2-CHa), 2.70 (1H, m, 2-CHb), 2.95-3.30 (2H, m, 3-CH_2), 3.90 (3H, s, Mc), 7.40 (1H, d, J= 8 Hz, 4-CH), 7.82 (1H, s, 7-CH), 7.98 (1H, d, J= 8 Hz, 5-CH).

1-Aminoindan-1,6-dicarboxylic acid (9)



A mixture of 8 (0.790 g, 3.04 mmol), $Ba(OH)_2$ octahydrate (0.632 g, 2.07 mmol) and water (11.5 ml) was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with water (30 ml) and extracted with CH_2Cl_2 (3x20 ml). CO_2 was then bubbled into the aqueous layer, the resulting precipitate was centrifuged and the supernatant was neutralized with 3N HCl. The neutral solution was submitted to ion exchange resin chromatography on Dowex 50x2 200 and elution with 10% pyridine to give a solid which was further purified by reversed phase medium pressure chromatography: elution with MeOH-water 6:4 afforded 9 (0.210 g, 30%) as a white solid, mp>300°C; ^{1}H-NMR (D_2O) δ 2.28 (1H, m, 2-CHa), 2.72 (1H, m, 2-CHb), 3.08 (2H, t, J= 6 Hz, 3-CH_2), 7.35 (1H, d, J= 8 Hz, 4-CH), 7.82 (1H, s, 7-CH), 7.85 (1H, d, J= 8 Hz, 5-CH); ^{13}C-NMR (D_2O) δ30.30, 35.00, 68.54, 124.67, 125.93, 129.26, 131.90, 138.55, 151.10, 169.60, 173.32.

EXAMPLE 2

4- and 5-Chloromethyl-indan (10)

Concentrated H_2SO_4 (90 ml) was added dropwise during 4 h to a warm (60°C), mechanically stirred solution of indan (77.2 g, 0.65 mol), formaldehyde (81 ml of a 40% solution) and 12N HCl (138 ml). After addition completion, stirring was continued for 6 h after which the reaction mixture was poured into water (1.5 l) and extracted with ether (4x300 ml). The combined organic phases were washed with water (3x50 ml) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue (80 g) was distilled in high vacuum to afford 10 (68.0 g, 63%), bp 75-80°C/0.3 mmHg; ^{1}H-NMR ($CDCl_3$) δ 2.10 (2H, m, 2-CH_2), 2.92 (4H, t, 1 - and 3-CH_2), 4.56 (2H, s, CH_2Cl), 7.18 (3H, m, aromatic's).

4- and 5-Acetoxymethyl-indan (11)

A suspension of 10 (68.0 g, 0.4 mol) and anhydrous AcONa (83.0 g, 0.6 mol) in glacial AcOH (200 ml) was heated at 150°C under vigorous mechanical stirring for 8 h. AcOH was then distilled off at reduced pressure (water pump) and the residue was taken up in water (200 ml) and extracted with AcOEt (2x100 ml). The combined organic phases were washed with water (2x50 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 11 (72.0 g, 92%) which was used in the next step without any further purification.

4- and 5-Indanyl methanol (12)

A solution of 11 (70.0 g, 0.37 mol) in 3.7N NaOH (120 ml) and MeOH (120 ml) was heated at 50°C under magnetic stirring for 0.5 H. MeOH was then partially removed at reduced pressure, the resulting mixture was poured

into cold (0°C) water and the solid thus formed was filtered (54 g) and dissolved in boiling light petroleum (300 ml). After cooling, the precipitate was removed and the mother liquid was evaporated to give **12** (11.0 g, 20%) as a mixture enriched in the desired α-isomer; ^{1}H-NMR ($CDCl_3$) δ 2.10 (2H, m, 2-CH_2), 2.80 (4H, m, 1- and 3-CH_2), 3.20 (1H, br, s, OH), 4.50 (2H, s, CH_2OH), 7.08 (3H, m, aromatic's).

Indan-4-carbaldehyde (13)

A solution of **12** (9.0 g, 61 mmol) in CH_2Cl_2 (150 ml) was added dropwise in 5 min to a mechanically stirred solution of pyridinium chlorochromate (13.1 g, 61 mmol) in CH_2Cl_2 (50 ml) in an argon atmosphere at room temperature. Stirring was continued for 2 h after which the reaction mixture was filtered with the aid of celite, the filtrate was washed with water (3x50 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was submitted to flash chromatography: elution with cyclohexane-ether 95:5 afforded **13** (2.6 g, 29%); ^{1}H-NMR ($CDCl_3$) δ 2.13 (2H, m, 2-CH_2), 2.91 (2H, t, J=7.4 Hz, 1-CH_2), 3.25 (2H, t, J=7.4 Hz, 3-CH_2), 7.29 (1H, 2d, J=7.6 Hz, 6-CH), 7.45 (1H, d, J=7.6 Hz, 7-CH), 7.60 (1H, d, J=7.6 Hz, 5-CH), 10.14 (1H, s, CHO). Following elution with the same solvent afforded a mixture of both formyl derivatives (6 g).

Indan-4-carboxylic acid (14)

Jones reagent (15 ml) was added dropwise in 15 min. to a magnetically stirred solution of **13** (1.1 g, 7.53 mmol) in acetone (50 ml) at room temperature. Stirring was continued for 1 h after which the reaction mixture was filtered and the solvent evaporated off. The residue was taken up in AcOEt (100 ml), washed with water (2x40 ml), brine (40 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded **14** (1.0 g, 82%) which was used in the next step without any further purification.

Methyl indan-4-carboxylate (15)

An etheral solution of diazomethane (35 ml, from 6.3 g of Diazald) was added dropwise in 15 min. to a cold (0°C) solution of 14 (2.5 g, 15.4 mmol) in ether (15 ml). After addition completion, stirring was continued for 10 min. at room temperature. Evaporation of the solvent gave 15 (2.5 g, 92%) which was used in the next step without any further purification; ^{1}H-NMR ($CDCl_3$) δ 2.06 (2H, m, 2-CH_2), 2.89 (2H, t, J=7.6 Hz, 1-CH_2), 3.24 (2H, t, J=7.6 Hz, 3-CH_2), 3.83 (3H, s, Me), 7.20 (1H, t, J=7.6 Hz, 6-CH), 7.37 (1H, d, J=7.6 Hz, 7-CH), 7.83 (1H, d, J=7.6 Hz, 5-CH).

Methyl 1-oxoindan-4-carboxylate (16)

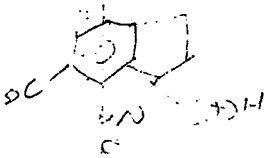
A solution of chromic anhydride (5.8 g, 58 mmol) in water (10 ml) was added dropwise in 10 min to a magnetically stirred solution of 15 (2.5 g, 14.2 mmol) in glacial AcOH (34 ml). Stirring was continued for 40 h after which the reaction mixture was poured into water (60 ml) and extracted with AcOEt (4x50 ml). The combined organic phases were washed with 10% K_2CO_3 (2x40 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a residue (1.5 g) which was submitted to flash chromatography: elution with light petroleum containing 5-15% AcOEt afforded 16 (0.3 g, 11%), mp 102°C; ^{1}H-NMR ($CDCl_3$) δ 2.72 (2H, m, 2-CH_2), 3.50 (2H, m, 3-CH_2), 3.96 (3H, s, Me), 7.48 (1H, 2d, J=7.6 Hz, 6-CH), 7.95 (1H, d, J=7.6 Hz, 7-CH), 8.28 (1H, d, J=7.6 Hz, 5-CH).

Hydantoin of 16 (17)

NaCN (0.207 g, 4.22 mmol) and $(NH_4)_2CO_3$ (0.87 g, 9.0 mmol) were added to a solution of 16 (0.40 g, 2.1 mmol) in DMF (4 ml) and water (0.4 ml) and the resulting mixture was heated at 120°C in a bomb for 3 h. After cooling,

the reaction mixture was poured into water (50 ml) and extracted with ether (5x20 ml). The combined organic phases were washed with water (2x20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (0.3 g) which was submitted to flash chromatography: elution with AcOEt-light petroleum 7:3 afforded 17 (0.20 g, 37%), mp 170-2°C (H_2O); ^{1}H-NMR ($CDCl_3$+CD_3OD) δ 2.30 (1H, m, 2-CHa), 2.72 (1H, m, 2-CHb), 3.47 (2H, m, 3-CH_2), 3.92 (3H, s, Me), 4.00 (2H, br s, 2xNH), 7.38 (2H, m, 6- and 7-CH), 7.98 (1H, m, 5-CH).

1-Aminoindan-1,4-dicarboxylic acid (18)



A suspension of 17 (0.15 g, 0.58 mmol) and $Ba(OH)_2.8H_2O$ (0.11 g, 0.35 mmol) in water (4 ml) was heated in a bomb at 120°C for 2.5 h. After cooling, the reaction mixture was filtered, the solid washed with CH_2Cl_2 (10 ml) and the filtrate evaporated to dryness in vacuo. The residue thus obtained (0.12 g) was submitted to ion exchange resin chromatography on Dowex 1x8 200: elution with 0.3N AcOH afforded 18 (0.040 g, 31%); ^{1}H-NMR (D_2O+HCl) δ 2.27 (1H, m, 2-CHa), 2.72 (1H, m, 2-CHb), 3.32 (2H, t, J=7.2 Hz, 3-CH_2), 7.30 (1H, 2d, J=7.7 Hz, 6-CH), 7.48 (1H, d, J=7.7 Hz, 7-CH), 7.87 (1H, d, J=7.7 Hz, 5-CH).

EXAMPLE 3

6-Acetyl-1,2,3,4-tetrahydronaphthalene (19)

$AlCl_3$ (15.3 g, 114.8 mmol) was added portionwise in 40 min. to a solution of 1,2,3,4-tetrahydronaphthalene (15.0 g, 113.5 mmol) and AcCl (8.9 g, 113.5 mmol) in benzene (45 ml) kept under vigorous magnetic stirring at 0°C in an argon atmosphere. The resulting mixture was reacted at room temperature for 30 min. after which cold (0°C) water was added (100 ml). The reaction mixture was then acidified with 3N HCl and extracted with AcOEt

(3x50 ml). The combined organic phases were washed with brine (60 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 19 as a yellow oil (20 g) which was used in the next step without any further purification.

1,2,3,4-Tetrahydronaphthalene-6-carboxylic acid (20)

Br_2 (71.8 g, 449 mmol) was added to a cold (0°C), magnetically stirred solution of KOH (84.43 g, 1.507 mol) in water (200 ml). 19 (20 g) was added dropwise in 15 min. to this solution and the resulting mixture was heated at 40°C under stirring for 3 h. The reaction mixture was then washed with ether (3x60 ml), the aqueous layer was acidified with 6N HCl and extracted with $CHCl_3$ (5x50 ml). The combined organic phases were washed with water (100 ml), brine (100 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 20 as an oil (13.5 g) which was used in the next step without any further purification.

Methyl-1,2,3,4-tetrahydronaphthalene-6-carboxylate (21)

An etheral solution of diazomethane (250 ml, from 44.5 g of Diazald ™) was added to a cold (0°C) solution of 20 (13.5 g) in ether (50 ml) and the resulting solution was magnetically stirred at room temperature for 30 min. Acetic acid (50 ml) was then added and the resulting mixture was washed with water (2x50 ml). Evaporation of the solvent gave a residue (13.5 g) which was submitted to flash chromatography: elution with light petroleum-AcOEt 9:1 afforded 21 (9.1 g) as a yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.80 (4H, m, 2-CH_2 and 3-CH_2), 2.80 (4H, m, 1-CH_2 and 4-CH_2), 3.90 (3H, s, Me), 7.08 (1H, d, J=9 Hz, 8-CH), 7.72 (1H, d, J=9 Hz, 7-CH), 7.75 (1H, s, 5-CH).

Methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-6-carboxylate (22) and methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-7-carboxylate (23)

A solution of Cr_2O_3 (14.9 g, 149 mmol) in glacial AcOH (43 ml) and water (13.5 ml) was added dropwise in 30 min. to a magnetically stirred solution of 21 (9.1 g, 47.9 mmol) in glacial AcOH (21.6 ml) at room temperature. Stirring was continued for 36 h after which the reaction mixture was diluted with water (100 ml) and extracted with AcOEt (4x50 ml). The combined organic phases were washed with 10% K_2CO_3 (2x50 ml), brine (50 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (8.5 g) which upon flash filtration on silica gel allowed the recovery of starting material 21 (1 g) and of a mixture of 22 and 23 (7 g). This mixture was then submitted to medium pressure chromatography: elution with light petroleum-AcOEt 85:15 yielded 22 (2.0 g, 20.5%); ^{1}H-NMR ($CDCl_3$) δ 2.13 (2H, m, 3-CH_2), 2.65 (2H, t, J=7.5 Hz, 2-CH_2), 3.00 (2H, t, J=7.5 Hz, 4-CH_2), 3.90 (3H, s, Me), 7.85 (1H, d, J=8 Hz, 8-CH), 7.90 (1H, s, 5-CH), 8.02 (1H, d, J=8 Hz, 7-CH). Further elution with the same solvent gave 23 (2.3 g, 23.5%); ^{1}H-NMR ($CDCl_3$) δ 2.15 (2H, m, 3-CH_2), 2.68 (2H, t, J=7.5 Hz, 2-CH_2), 3.02 (2H, t, J=7.5 Hz, 4-CH_2), 3.92 (3H, s, Me), 7.33 (1H, d, J=8 Hz, 5-CH), 8.10 (1H, 2d, J=8 Hz, J=2 Hz, 6-CH), 8.66 (1H, d, J=2 Hz, 8-CH).

Hydantoin of (22) (24)

NaCN (0.231 g, 4.7 mmol) and $(NH_4)_2CO_3$ (0.971 g, 10.07 mmol) were added to a solution of 22 (0.479 g, 2.35 mmol) in DMF (4.5 ml) and water (0.5 ml) and the resulting mixture was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with AcOEt (30 ml), washed with saturated Na_2CO_3 (5x20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (0.5 g) was submitted to flash chromatography: elution with $CHCl_3$-MeOH 98:2 yielded 24 (0.360 g, 59%); ^{1}H-NMR ($CDCl_3$) δ 1.80 and 2.10 (2H, 2m, 3-CH_2), 2.35 (2H, m, 2-

CH_2), 2.90 (2H, m, 4-CH_2), 3.90 (3H, s, Me), 7.24 (1H, s, 5-CH), 7.27 (1H, m, 8-CH), 7.82 (1H, m, 7-CH).

1-Amino-1,2,3,4-tetrahydronaphtalene-1,6-dicarboxylic acid (25)

A mixture of 24 (0.360 g, 1.39 mmol), $Ba(OH)_2$ octahydrate (0.413 g, 1.35 mmol) and water (5 ml) was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3x15 ml). CO_2 was then bubbled into the aqueous layer, the resulting precipitate was centrifuged and the supernatant was neutralized with 3N HCl. The neutral solution was submitted to ion exchange resin chromatography on Dowex 50x2 200 and elution with 10% pyridine to give a solid which was further purified by preparative t.l.c.: elution with nBuOH-AcOH-H_2O (68:16:16) afforded 25 (0.100 g, 33%); ^{1}H-NMR (D_2O) δ 1.75 and 1.90 (2H, m, 3-CH_2), 2.10 and 2.30 (2H, m, 2-CH_2), 2.70 (2H, m, 4-CH_2), 7.20 (1H, d, 8-CH), 7.55 (2H, m, 5- and 7-CH); ^{13}C-NMR (D_2O) δ 18.67, 28.97, 32.44, 61.81, 128.20, 128.71, 131.64, 132.32, 135.90, 139.88, 170.38, 174.55.

Methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-6-carboxylate (22) and methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-7-carboxylate (23)

A solution of Cr_2O_3 (14.9 g, 149 mmol) in glacial AcOH (43 ml) and water (13.5 ml) was added dropwise in 30 min. to a magnetically stirred solution of 21 (9.1 g, 47.9 mmol) in glacial AcOH (21.6 ml) at room temperature. Stirring was continued for 36 h after which the reaction mixture was diluted with water (100 ml) and extracted with AcOEt (4x50 ml). The combined organic phases were washed with 10% K_2CO_3 (2x50 ml), brine (50 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (8.5 g) which upon flash filtration on silica gel allowed the recovery of starting material 21 (1 g) and of a mixture of 22 and 23 (7 g). This mixture was then submitted to medium pressure chromatography: elution with light petroleum-AcOEt 85:15 yielded 22 (2.0 g, 20.5%); ^{1}H-NMR ($CDCl_3$) δ 2.13 (2H, m, 3-CH_2), 2.65 (2H, t, J=7.5 Hz, 2-CH_2), 3.00 (2H, t, J=7.5 Hz, 4-CH_2), 3.90 (3H, s, Me), 7.85 (1H, d, J=8 Hz, 8-CH), 7.90 (1H, s, 5-CH), 8.02 (1H, d, J=8 Hz, 7-CH). Further elution with the same solvent gave 23 (2.3 g, 23.5%); ^{1}H-NMR ($CDCl_3$) δ 2.15 (2H, m, 3-CH_2), 2.68 (2H, t, J=7.5 Hz, 2-CH_2), 3.02 (2H, t, J=7.5 Hz, 4-CH_2), 3.92 (3H, s, Me), 7.33 (1H, d, J=8 Hz, 5-CH), 8.10 (1H, 2d, J=8 Hz, J=2 Hz, 6-CH), 8.66 (1H, d, J=2 Hz, 8-CH).

Hydantoin of (22) (24)

NaCN (0.231 g, 4.7 mmol) and $(NH_4)_2CO_3$ (0.971 g, 10.07 mmol) were added to a solution of 22 (0.479 g, 2.35 mmol) in DMF (4.5 ml) and water (0.5 ml) and the resulting mixture was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with AcOEt (30 ml), washed with saturated Na_2CO_3 (5x20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (0.5 g) was submitted to flash chromatography: elution with $CHCl_3$-MeOH 98:2 yielded 24 (0.360 g, 59%); ^{1}H-NMR ($CDCl_3$) δ 1.80 and 2.10 (2H, 2m, 3-CH_2), 2.35 (2H, m, 2-

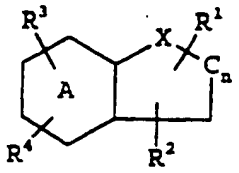
CH_2), 2.90 (2H, m, 4-CH_2), 3.90 (3H, s, Me), 7.24 (1H, s, 5-CH), 7.27 (1H, m, 8-CH), 7.82 (1H, m, 7-CH).

1-Amino-1,2,3,4-tetrahydronaphtalene-1,6-dicarboxylic acid (25)

A mixture of 24 (0.360 g, 1.39 mmol), $Ba(OH)_2$ octahydrate (0.413 g, 1.35 mmol) and water (5 ml) was heated at 120°C in a bomb for 3 h. After cooling, the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3x15 ml). CO_2 was then bubbled into the aqueous layer, the resulting precipitate was centrifuged and the supernatant was neutralized with 3N HCl. The neutral solution was submitted to ion exchange resin chromatography on Dowex 50x2 200 and elution with 10% pyridine to give a solid which was further purified by preparative t.l.c.: elution with nBuOH-AcOH-H_2O (68:16:16) afforded 25 (0.100 g, 33%); ^{1}H-NMR (D_2O) δ 1.75 and 1.90 (2H, m, 3-CH_2), 2.10 and 2.30 (2H, m, 2-CH_2), 2.70 (2H, m, 4-CH_2), 7.20 (1H, d, 8-CH), 7.55 (2H, m, 5- and 7-CH); ^{13}C-NMR (D_2O) δ 18.67, 28.97, 32.44, 61.81, 128.20, 128.71, 131.64, 132.32, 135.90, 139.88, 170.38, 174.55.

Claims

1. A compound of formula I



(I)

wherein

n is 0, 1 or 2; and

X is -O-, -S, -N(R^5)- or -CH_2-; and

R^1 is H, NH_2, NHR^5 or OH; and

R^2 and R^3 independently are H, COOH, $COOR^5$, $CONH_2$, $CONHR^5$, $CON(R^5)_2$, $CONHSO_2R^5$ or tetrazole; and

R^4 is H, OH, NH_2, NHR^5, CF_3, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, phenyl or C_{1-4}-alkoxy; and

R^5 is H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenyl or C_{3-6}-cycloalkyl; and

ring A can be partly or completely saturated or aromatic,

or a salt thereof with a pharmaceutically acceptable acid or base.

2. A compound according to claim 1 selected from the following:

1-Aminoindan-1,5-dicarboxylic acid,

1-Aminoindan-1,6-dicarboxylic acid,

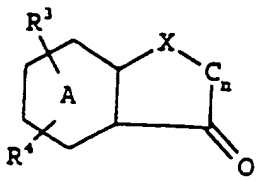
1-Aminoindan-1,4-dicarboxylic acid,

1-Amino-1,2,3,4-tetrahydronaphtalene-1,6-dicarboxylic acid,

or a salt thereof with a pharmaceutically acceptable acid or base.

3. A method of preparing a compound according to claim 1, CHARACTERIZED IN

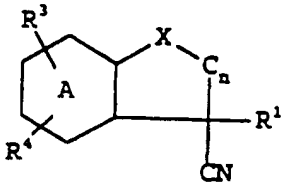
a) reacting a compound of the formula II



(II)

prepared by well known methods, wherein X, n, R^3, R^4 have the meanings defined above with reagents well known for converting oxo groups to amino acids or hydroxy acids either through hydantoin formation, through hydroxy nitrile or through aminonitrile formation, or

b) reacting a compound of the formula III



(III)

wherein X, n, R^1, R^3 and R^4 have the meanings defined above with reagents known to transform a cyano group into a R^2 group wherein R^2 has the meaning defined above provided that R^2 must not be H.

4. A pharmaceutical composition comprising a compound according to

claim 1 together with a pharmaceutically acceptable carrier or diluent.

5. A pharmaceutical composition for use in treating a disease in the central nervous system related to the metabotropic glutamate receptor system comprising an effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier or diluent.

6. The pharmaceutical composition according to claim 4 or 5 in the form of an oral dosage unit or parenteral dosage unit.

7. The pharmaceutical composition according to claim 6, wherein said dosage unit comprises from about 1 to about 100 mg of the compound according to claim 1.

8. A method of treating a disease in the central nervous system related to the metabotropic glutamate receptor system comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

9. A method of treating a disease in the central nervous system related to the metabotropic glutamate receptor system comprising administering to a subject in need thereof a pharmaceutical composition according to claim 5.

10. The use of a compound according to claim 1 for the preparation of a medicament for treatment of a disease in the central nervous system related to the metabotropic glutamate receptor system.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00421

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 229/46, C07C 229/50, C07D 307/87, C07D 333/62, C07D 257/04, A61K 31/195, A61K 31/19, A61K 31/38, A61K 31/34, A61K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO, A1, 9504713 (THE UPJOHN COMPANY), 16 February 1995 (16.02.95) --	1-7,10
X	EP, A2, 0077122 (IMPERIAL CHEMICAL INDUSTRIES PLC), 20 April 1983 (20.04.83), page 15, line 33 - page 16, line 19, the examples; the claims --	1-7,10
X	EP, A1, 0399982 (AKTIEBOLAGET ASTRA), 28 November 1990 (28.11.90) --	1-7,10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 1995	26 -06- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00421

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 9015047 (THE UPJOHN COMPANY), 13 December 1990 (13.12.90), page 8, line 8 - line 28, the claims	1-7,10
X	US, A, 4018817 (SHUNSAKU NOGUCHI ET AL), 19 April 1977 (19.04.77), column 1, line 5 - line 40	1-7
X	EP, A1, 0118564 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD), 19 Sept 1984 (19.09.84)	1-7
X	WO, A1, 9007490 (THE UPJOHN COMPANY), 12 July 1990 (12.07.90), page 6, line 4 - line 23, the claims	1-7,10
X	STN International, File CA, volume 114, no. 19, 13 May 1991, (Columbus Ohio, US),Ma, Shenqxing et al: "Dopaninerqic structure-activity relationships of 2-aminoindans and cardiovascular action and dopaminerqic activity of 4-hydroxy, 5-methyl, 2-di-N-propylaminoindan (RD-211), abstract no. 177884, & J. Pharmacool. Exp. Ther. (1991), 256 (2) 751-6	1-7
X	STN International, File CA, volume 87, no 21, 21 November 1977,(Columbus Ohio, US), Sundeen, Joseph E. et al: "Selective inhibition of the monosynaptic spinal reflex by a serier of hydroxylated alkylaminoindans", abstract no. 161428, & J. Med. Chem. (1977), 20 (11), 1478-85	1-7
X	STN International, File Medline, STN accession no. 87011614, Cannon J G et al: "Assement of a potential dopaminerqic prodrug in several ring systems", J Med Chem (1986 Oct) 29 (10) 2016-20	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00421

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEM.PHARM.BULL., Volume 14, No 4, 1966, Shunsaku Shiotani et al, "Studies on Diazabenzobicyclo 3.3.1 nonane System. IV Synthesis of 1,2,3,4,5,6-Hexahydro-1, 5-methanobenzo e 1,3 diazocine Derivatives", page 324 - page 329, see page 325, compounds II,IV --	1-3
X	STN International, File CA, volume 80, no. 21, 27 May 1964 (Columbus Ohio, US), Edlund Ulf: "Preparation of some N-substituted 2-aminoindans", abstract no. 120604, & Acta Chem. Scand. (1973), 27 (10) , 4027-9 --	1,3
X	JOURNAL OF PHARMACEUTICAL SCIENCES, Volume 52, 1963, William H. Shelver et al, "Some 2-Substituted Derivatives of 2-Dimethylamino-1,2,3, 4-tetrahydronaphthalene", page 250 - page 252, see page 250, second paragraph -- --------	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00421

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8,9
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/95

International application No.
PCT/DK 94/00421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9504713	16/02/95	NONE	
EP-A2- 0077122	20/04/83	SE-T3- 0077122	
		AU-B- 566342	15/10/87
		AU-A- 8801482	24/03/83
		CA-A- 1257746	18/07/89
		JP-A- 58069852	26/04/83
		US-A- 4464358	07/08/84
EP-A1- 0399982	28/11/90	AU-B- 644081	02/12/93
		AU-A- 5818590	18/12/90
		CA-A- 2032498	27/11/90
		CN-A- 1047494	05/12/90
		JP-T- 4500362	23/01/92
		NO-B- 176603	23/01/95
		PL-B- 165166	30/11/94
		WO-A- 9014330	29/11/90
WO-A1- 9015047	13/12/90	AU-B- 654653	17/11/94
		AU-A- 5822190	07/01/91
		CA-A,A- 2051399	01/12/90
		EP-A- 0476016	25/03/92
		JP-T- 4505618	01/10/92
		NO-B,C- 176437	27/12/94
US-A- 4018817	19/04/77	AU-A- 6333473	12/06/75
		BE-A,A- 808376	07/06/74
		CA-A- 1018161	27/09/77
		CH-A- 591431	15/09/77
		DE-A,C,C 2359537	12/06/74
		FR-A,B- 2209748	05/07/74
		GB-A- 1392270	30/04/75
		JP-C- 1083834	25/02/82
		JP-A- 49080054	02/08/74
		JP-B- 56023982	03/06/81
		NL-A- 7316834	11/06/74
		SE-B,C- 407568	02/04/79

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/95

International application No.
PCT/DK 94/00421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0118564	19/09/84	SE-T3- 0118564	
		EP-A,B- 0118565	19/09/84
		SE-T3- 0118565	
		JP-B- 1012746	02/03/89
		JP-C- 1539177	16/01/90
		JP-A- 59044347	12/03/84
		US-A- 4546107	08/10/85
		US-A- 4598093	01/07/86
		WO-A- 8400957	15/03/84
		WO-A- 8400961	15/03/84
		DE-A- 3337305	19/04/84
		GB-A- 2128348	26/04/84
		JP-C- 1439942	19/05/88
		JP-A- 59044357	12/03/84
		JP-B- 62050463	24/10/87
WO-A1- 9007490	12/07/90	AT-T- 113271	15/11/94
		AU-A- 4844290	01/08/90
		CA-A- 2026775	10/07/90
		DE-D,T- 69013672	30/03/95
		EP-A,B- 0452390	23/10/91
		SE-T3- 0452390	
		JP-T- 4502620	14/05/92
		US-A- 5225596	06/07/93